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RAPID PUBLICATION
CLINICAL AND LOCUS HETEROGENEITY IN BRACHYDACTYLY TYPE C

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Brachydactyly type C is characterized by shortness of the second and fifth middle phalanges and the first metacarpal. It is inherited as an autosomal dominant trait, and is noted for its widely variable clinical phenotype both within and between families. In most families involvement is limited to the hands. However, in some families additional skeletal and non-skeletal findings have been reported. We report on 12 affected members from a 5 generation kindred that segregates a brachydactyly type C phenotype. All affected individuals had shortness principally affecting the second and fifth phalanges and first metacarpal. However, the metacarpal-phalangeal profile indicated that other digital elements were short as well. In addition, one affected individual had a bilateral Madelung deformity, but none had foot involvement. No other non-skeletal findings co-segregated with brachydactyly in this family.

Recently, a gene for brachydactyly type C has been localized to 12q24. This was done by studying a large kindred first reported by Haws [1963], which manifests both hand and foot anomalies. Here we present linkage data which excludes the 12q24 locus in our kindred, indicating locus heterogeneity as one explanation for the interfamilial variability described in brachydactyly type C.

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INTRODUCTION

Brachydactyly is shortness of one or more digits due to an abnormality in the development of the phalanges and/or metacarpals. It is seen as one finding in over 135 skeletal dysplasias and multiple congenital anomaly syndromes, or it can occur as an isolated anomaly [Temtamy and McKusick, 1978; Winter et al., 1993]. As an isolated anomaly, brachydactyly is most commonly an autosomal dominant disorder, with markedly variable expressivity [Winter et al., 1993]. Isolated brachydactyly has been divided into a number of phenotypically distinct sub-types based on which bones and which digits are most characteristically involved (Table I) [Bell, 1951; Fitch, 1979]. Brachydactyly type C is characterized by shortness of the second and fifth middle phalanges (MP) and the first metacarpal (MC) [Bell, 1951; Temtamy and McKusick, 1978]. In addition, specific to brachydactyly type C is the occasional finding of "hypersegmentation" of digits 2 and 3 [Drinkwater, 1916]. This apparently extra bone is not a true extra phalanx, as there is no growth plate. Rather, it is an abnormally large proximal epiphyseal center. In most cases, this will fuse with the metaphysis sometime after puberty and form a large, misshapen proximal phalanx,

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TABLE I. The Classification of Isolated Brachydactyly by Bell [1951] and Fitch [1979]

Bell	Fitch	Characteristic Anomalies[1]	Other Findings/Comments
A-1	Type 9	Hypoplasia of MP H/F, may involve all tubular bones of H/F; hypoplasia proximal phalanx; I relative size of digits preserved (III>IV>II>V)	Abnormalities of distal radius, tibia, femoral/humeral head, acetabulum/ glenoid fossa; hypoplasia ulna styloid; short stature
A-2	Type 2	Hypoplastic MP II of h	Remaining bones are normal except for occasional clinodactyly finger V
A-3	Type 3	Hypoplasia MP V +/- clinodactyly	Considered normal variant
A-4	(considered variable manifestation of Type 9)	Hypoplasia MP II and V	
A-5	(considered variable manifestation of Type 8)	Absent MP; nail hypoplasia	
B	Type 8	Hypoplasia/absence of TP II-V; nail hypoplasia	IV and V usually more severe than II and III
C	Type 11	Hypoplasia MP II-V, MC as well (primarily I),can see "extra digit" II, III; digit IV is usually spared	Clinically very variable; short stature, foot anomalies, other skeletal (hips, vertebrae, humerus, radius, ulna) can be seen in some families; non-penetrance vs. germ-line mosaicism reported [Baraitser and Burn, 1983]
D	Type 1	Hypoplasia TP I; "stump thumb"	Considered normal variant
E	(sub-classified)	Short MC +/- MT IV	Heterogeneous
	Type 4	Short MC II	
	Type 5	Short MC IV	
	Type 6	Short MT IV	
	Type 7	Short MC and MT IV	
	Type 10	Short MC and DP, short stature	

[1] MP: middle phalanges; H/F: hands and/or feet; TP: terminal phalanges; MC: metacarpal; MT: metatarsal; DP: distal phalanx

with a radial protuberance that causes the digit to be ulnar deviated. The enlarged epiphysis often retains a sclerotic line on X-ray at the site of fusion [Rimoin et al., 1974].

Brachydactyly type C is a clinically variable disorder. At times, this may cause diagnostic confusion, especially with brachydactyly type A-1, as both conditions may present with shortness of the proximal and middle phalanges. However, in brachydactyly type A-1 the first metacarpal is not short, and the size of the shortened digits follows the normal state, with the shortest digit being the

fifth, followed by the second, the fourth, and third finger. In brachydactyly type C, the fourth digit is the least affected, and is therefore longer than the third [Bell, 1951; Cloherty, 1969; Herrmann, 1974; Fitch, 1979].

In most families with brachydactyly type C, anomalies are limited to the hands [Bell, 1951], but associated abnormalities have been reported. These include a variety of foot anomalies [McNutt, 1946; Haws, 1963; Rowe-Jones et al., 1992], hip dysplasia [Robinson et al., 1968], short stature [Fitch et al., 1979], and variable epiphyseal abnormalities [Rennel and Steinbach, 1970; Steinbach and Brown, 1969]. In addition, cupped ears segregated with the condition in one family [Rowe-Jones et al., 1992].

While distinguishing characteristics are clinically very useful in differentiating the brachydactyly subtypes, it is unclear if these differences are relevant to the molecular genetics of these conditions. Such questions are beginning to be addressed. Studying the large family originally described by Haws [1963], Polymeropoulos et al. [1996] reported linkage of brachydactyly type C to 12q24. This represents the second kindred with an autosomal dominant brachydactyly disorder to be mapped; brachydactyly associated with severe hypertension has been mapped to chromosome 12p [Schuster et al., 1996].

Here we report on the clinical findings of 12 members of a five-generation family that also segregates brachydactyly type C. While this family shared many findings with the family reported by Haws [1963], clinical differences are evident as well. In previous reports, such differences have been ascribed to the well-recognized wide clinical variability of brachydactyly type C. However, our linkage data suggests another possibility, as we demonstrate that the brachydactyly C locus in this family does not map to 12q24. Thus, in some cases, the interfamilial clinical variability in brachydactyly type C may be due to locus heterogeneity.

CLINICAL REPORT

The family was ascertained through the Genetics Clinic of the Center for Human Genetics. The proposita, individual IV-17, is a 53-year-old woman who works in a supervisory position for local government. She is in good health, and has an unremarkable past medical history. Her small hands were noted during childhood, and recognized as a "family trait" that could be traced back to her grandfather (II-2) and was present in many members of her extended family (Fig. 1). Her physical examination was normal except for the hand findings. Her height was 160 cm (25th centile), and she had a normal facial appearance and normal feet (length: 23 cm, 25th centile). Her hands were symmetrically small, with a single palmar crease. Her palm length was 9.3 cm (3rd centile), middle finger 7 cm (<3rd centile).

A total of 25 individuals from this family was evaluated through interviews, review of available medical records, and radiographic examination. AP radiographs of the hands and feet were done on all available individuals; additional extremity films were done in certain patients. Caliper measurements of the lengths of the 19 tubular bones of the hand were compared to normative data [Garn et al., 1972] to produce a metacarpal phalangeal pattern profile [Poznanski, 1986]. Axial measurements of each bone were performed along the maximum longitudinal axis of all the bones of the hand (except the base of the third metacarpal where the extra length of the styloid process is ignored). In children, the total bone length also includes the epiphysis.

Twelve individuals were found to be affected. Representative hand films are shown in Fig. 2a-f. The most striking finding on visual inspection of the radiographs was shortness of the second and fifth middle phalanges (MP) and first metacarpal (MC). Unlike other described families, shortness of the third proximal phalanx (PP) and MP was not as prominent as that seen in the second digit. One individual (V-9, Fig. 2e) manifests

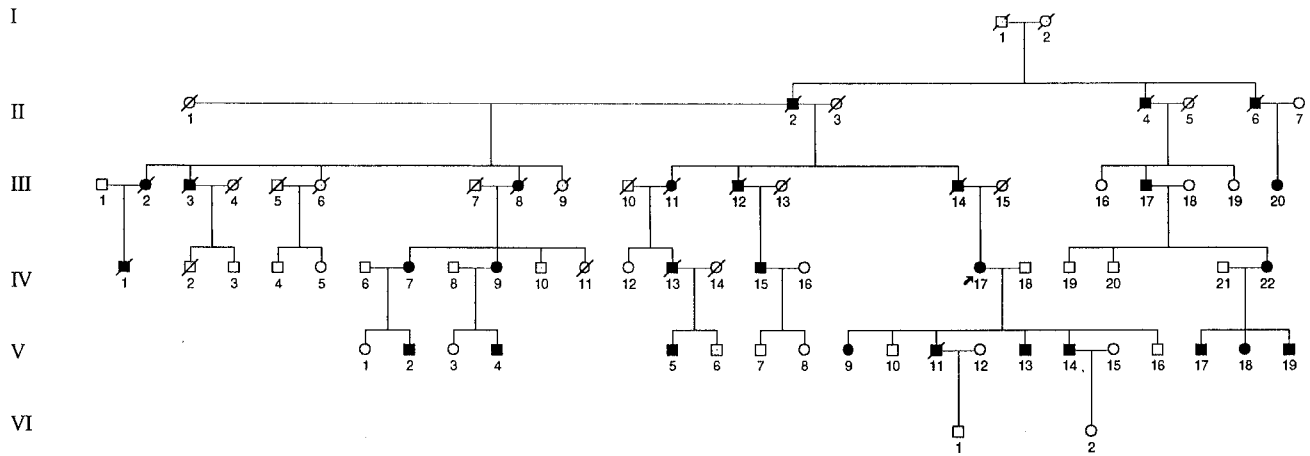

Fig. 1 Pedigree of family. Solid symbols represent affected individuals

TABLE II. Clinical Findings in Affected Individuals

			Metacarpal length (-SD)[a]					Proximal phalanx length					Middle phalanx length					
Patient	Age	Height (cm)/ centile	1	2	3	4	5	1	2	3	4	5	2	3	4	5	Extra bone[b]	Other skeletal findings
III.17	78 yr	162.5/<5th	4.3	3.6	4.2	4.3	4.0	3.2	5.3	13	2.8	2.7	13	9.4	6.6	7.9	+	
III.20	82 yr	163/ 40th	4.3	1.6	2.2	2.3	3.0	0.7	1.3	2.6	0.8	1.3	8.9	6.4	3.7	3.9	+	
IV.7	80 yr	164.5/50th	4.3	1.7	2.2	2.9	2.8	1.2	1.3	1.3	1.2	+2.9	7.0	5.8	2.6	3.9	-	
IV.9	46 yr	161/30th	4.7	2.1	2.6	4.0	1.4	1.2	0.9	2.2	1.2	0.8	7	6.4	3.2	5.1	-	
IV.17	53 yr	160/25th	9.3	2.5	3.2	2.9	3.0	1.7	1.7	1.7	0.8	1.3	6.4	4.6	3.2	6.3	+	
IV.22	42 yr	152/<5th	4.0	2.1	2.9	2.6	2.8	2.7	3.9	4.8	2.0	2.4	11	8.2	4.9	6.9	-	
V.2	24 yr	170.5/30th	6.1	3.1	2.9	2.9	3.3	0.0	1.2	0.2	0.7	0.7	10.1	4.4	2.6	4.1		
V.5	26 yr	165/<5th	7.1	2.6	2.9	1.2	2.3	0.5	1.7	0.6	0.2	0.7	4.4	3.4	2.3	2.3	-	bilateral Madelung malformation
V.9	30 yr	155/5-10th	9.3	1.4	3.2	2.3	1.9	0.7	1.3	3.0	0.3	+0.4	11	S[c]	2.6	6.3	+	
V.17	13 yr	167.5/75-90th	1.2	+0.1	+0.1	+0.4	+0.1	+2.5	+1.6	+1.9	+1.9	+1.9	7.9	3.3	0.5	2.0	+	
V.18	11 yr	152.5/50th	3.2	4.4	1.1	1.3	1.8	1.4	0.7	0.2	+0.2	1.4	7.6	4.2	2.4	4.5	-	
V.19	9 yr	137/75-90th	4.0	+.1	1.3	2.2	1.8	0.7	+0.3	+1.2	+1.4	+0.5	8.4	4.3	2.2	6.9	+	

a. -SD: negative standard deviations; b. Any evidence that there was an extra bony segment-see text for full explanation; c. S: symphalangism MP-DP

Fig 2. a: Patient III-17. Note typical brachydactyly type C., including short MP of digits 2 and 5, normal fourth finger, and the radial protuberance at second metacarpophalangeal joint with ulnar deviation.

Fig. 2b: Patient IV-22. Note severely short second and fifth middle phalanges. Note prominent radial protuberance at second metacarpophalangeal joint with triangular shape and ulnar deviation.

Fig. 2e. Patient V-9: severely short first MC and MP of phalanges 2 and 5. Sclerotic line through broad and malformed third MP. Note separate ossification at base of right second PP, with sclerotic line at identical site on other hand.

Fig. 2c. Patient V-5: severe shortness of first MC and to a lesser extent the third, fourth and fifth MC.

Fig. 2d. Patient V-5, showing the Madelung malformation.

Fig. 2f. Patient V-19: 9-year-old boy shows short first MC and MP 2 (with sclerotic line) and 5, and short fourth MC.

"hypersegmentation", while in two other individuals a sclerotic line was evident in the second PP. Four individuals had a "radial protuberance" of the second metacarpal-phalangeal (MP) joint, and a triangular slope to the base of the PP with ulnar deviation (Fig. 2b). The joint space was normal.

While some bones were clearly shorter on visual inspection, systematic measurements of the 12 affected individuals (Table II) showed more generalized involvement of the bones in the hand. In all affected individuals, the second MP is short, ranging from 4.4 to 13 standard deviations below the mean (-SD), and the third and fifth MP were also consistently short (-2 to -9 SD). In many patients, the fourth MP was involved, but it was consistently the least affected MP.

The first MC was short in 11 of 12 affected individuals, ranging from -1.2 to -9.3 SD. The one individual (V-17) with a first MC in the normal range manifests other signs of brachydactyly type C, namely shortness of the second and fifth MP, and the "radial protuberance" of the second MCP joint [Fig. 2f]. While the first MC was the most severely shortened MC, 5 of 12 affected individuals had shortness (<-2.0 SD) of all MC, and 11 of 12 had shortness of 2 or more MCs.

In 2 of 12, all PP were short. In these 2 (III-17, IV-22) the third PP was the most affected. Three individuals (III-20, IV-9, V-9) also had short third PP without other PP involvement.

In all affected individuals, the distal phalanges were normal. One individual (V-5) had an associated skeletal finding, a bilateral Madelung anomaly. He had reported that he had "curved forearms". In no other affected individuals were there associated skeletal anomalies. In 7 affected individuals, foot radiographs were reviewed and no abnormalities were noted. Short stature was seen in some affected individuals in this family (< 3rd centile-see Table II). However, this did not segregate completely with the hand malformation. Other affected individuals had normal stature, and a number of unaffected individuals had heights at or below the 5th centile.

Only three children were present in this family, with the youngest age 9 years. We did not discover the youngest age at which this syndrome is radiographically diagnosable, but it was clearly present in the 9 year old child. In addition, the affected children had a normal bone age.

MOLECULAR STUDIES
MATERIALS AND METHODS

After obtaining informed consent, DNA was collected from members of the family. DNA extraction was performed with the Puregene kit (Gentra Systems®, Inc., Minneapolis, MN) following the manufacturer's protocol. Using primers flanking simple sequence repeat polymorphisms, PCR amplification of genomic DNA was performed in 10 μl volumes containing 37.5 ng DNA and 2 picomoles of each primer. Alleles were detected by end-labeling the forward primer with ^{33}P. PCR conditions included a 4 minute initial denaturation at 95°C, followed by 35 cycles of 94°C for 40 seconds, 55°C for 50 seconds, and 72°C for 50 seconds, with a final extension at 72°C for 7 minutes. Products were then denatured in 40% formamide and separated on denaturing polyacrylamide gels. Alleles were detected by autoradiography using 24-48 hour exposures. Two-point linkage analysis was performed using the LINKAGE software package [Lathrop et al., 1985]. Autosomal dominant inheritance with complete penetrance was assumed. The mutant gene frequency and phenocopy frequency in the general population were set at 10^{-5}. Equal allele frequencies were assumed for each marker locus. Sex-averaged recombination distances were taken from the Généthon human linkage map [Dib et al., 1996].

RESULTS

Twelve polymorphic markers spanning a 57 cM interval on human chromosome 12q24 were studied; these included 7 markers (12cen-D12S324-

D12S1679-D12S1659-D12S367-D12S1723-D12S1628-D12S357-12q tel) covering the 14 cM candidate region recently identified as containing a brachydactyly C locus [Polymeropoulos et al., 1996]. Two point lod scores did not demonstrate linkage in our kindred to any 12q24 marker. The entire 12q24 interval was recombinant in individual V-18, who is clearly affected. In this individual, the likelihood of a double recombinant event occurring between adjacent markers is less than 10^{-3}, providing strong evidence for exclusion of this region. Additional support derives from the observation that there was no evidence for sharing of an identical allele, or haplotype, among affected relatives separated from their common ancestor by 4-6 meioses (e.g. III- 20, IV- 7, IV-17, IV-22). Taken together, these data exclude the brachydactyly C interval identified by Polymeropoulos et al. [1996] as a candidate region in our kindred.

DISCUSSION

We report the clinical findings of 12 affected individuals from a family segregating brachydactyly type C. In addition, we show that the brachydactyly type C locus in this family is distinct from that in the family first reported by Haws [1963], which has been assigned to 12q24 [Polymeropoulos et al., 1996].

The clinical differences in this family, the family reported by Haws [1963], and a number of others has been attributed to the well-recognized widely variable phenotype associated with brachydactyly type C. One likely explanation for this is that alterations in more than one genetic locus can cause this phenotype. One could argue that this kindred, or that of Haws, does not actually have brachydactyly C; however, both families fulfill the accepted criteria for diagnosis, and have phenotypes atypical for another brachydactyly subgroup. It may be that much of what is thought to represent clinical variability of the same disorder simply represents mutations in different genes. Brachydactyly type C would join Holt-Oram [Terrett et al., 1994], Bardet-Biedl [Kwitek-Black et al., 1993; Leppert et al., 1994; Sheffield et al., 1994; Carmi et al., 1995]; and Pfeiffer syndromes [Robin et al., 1994; Muenke et al., 1994] among others, as a clinically defined condition that exhibits locus heterogeneity at the molecular level.

In the majority of families with brachydactyly type C, the abnormal findings are restricted to the hands [Bell, 1951]. However, a number of reports have documented families in which there are a variety of associated skeletal findings. These include short stature, hip dysplasia, anterior wedging of the vertebrae, decreasing interpedicular distance of the vertebrae, radio-ulnar and humeral-ulnar abnormalities, Madelung deformity, and other epiphyseal changes [Robinson et al., 1968; Steinbach and Brown, 1969; Rennel and Steinbach, 1970; Fitch et al., 1979]. Limb development is a complex event, orchestrated by a number of genes acting in concert. While it is apparent that mutations in at least two genes can cause the brachydactyly type C phenotype, it may be that this phenotype can be caused by mutations in other genes involved in this process.

Since the development of the lower limbs parallels the upper limb [Greulich and Pyle, 1959], why are the abnormalities in this and most brachydactyly C families be restricted to the hands? Perhaps this gene's expression pattern is limited to the upper limbs, or the mutation affects only upper limb development. However, it is interesting to note that the development of the upper limbs is 1-2 days ahead that of the lower limbs [Sadler, 1995]. Therefore, it may be that the deleterious effect of this mutation occurs at a very specific time in development, a period that is more crucial to the upper limbs than the lower limbs.

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